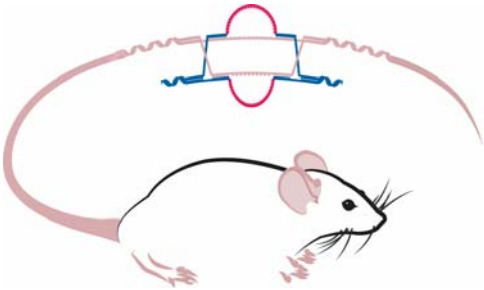

Knockout Mouse Project (KOMP)

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What is KOMP (the Knockout Mouse Project)?

The Knockout Mouse Project is a trans-NIH initiative that aims to generate a comprehensive and public resource comprised of mice containing a null mutation in every gene in the mouse genome. By capitalizing on efficiencies of scale and a centralized production effort, the project intends to make this catalog of mutants available in mouse strain C57BL/6 for two reasons: it the most widely used strain and it is the strain for which complete genome sequence has been made available. This concept for the KOMP was developed at an international workshop held at the Banbury Center in the autumn of 2003 (and published in Austin, et al., Nature Genetics, September 2004). The meeting attendees agreed that such a comprehensive resource of null mutants would greatly benefit the biomedical research community and enhance our understanding of human disease. Acting on the outcome of this meeting, the National Human Genome Research Institute (NHGRI) organized a working group of NIH Institute and Center representatives to plan the role that NIH should play in implementing this goal. In developing the NIH KOMP plan, this working group considered the current state of the field and recommendations from members of mouse research community made during a second workshop in March, 2005. (see http://www.genome.gov/15014549 for an executive summary).

In brief, the NIH KOMP initiative aims to: 1) support a mixture of two approaches to make the C57BL/6 resource of null alleles marked with a high utility reporter: a) a null mutant resource for as much of the genome as possible in C57BL/6 by either transposon mutagenesis or gene trapping and b) mutagenize the ~10,000 genes that have not yet been mutated, by gene targeting, also preferably in C57BL/6, by 2010; 2) support a repository to house the products of this resource as well as an additional 'repatriation' effort to bring into repositories 1000 of the existing high priority mouse knockouts not already stored in a public repository; 3) a technology

development effort that aims to increase the germ line transmission efficiency for C57Bl/6, so that it may be used in a high throughput capacity in generating this resource; and 4) a data coordination center which will make the results of the production effort available to the research community.

Links to the KOMP RFAs (issued September 2005)

1. **HG-05-007: The Completion of a Comprehensive Mouse Knockout Resource**

2. **DA-06-009: Development and Improvement of Inbred ES Cell Lines for Use in Generation of Mouse Mutants**

3. **HG-05-008: A Data Coordination Center for the Knockout Mouse Project (KOMP)**

4. **Repository and Repatriation RFA coming soon**

What is the utility of a large scale mouse mutagenesis effort?

Recent technological advances in molecular genetics now support large-scale production and analysis efforts of induced genetic mutations in model systems ranging from microorganisms to mammals. Rapidly elucidating gene function using these models has lead to insights about specific gene and genome-wide functional and regulatory relationships.

In addition to advancing the biological sciences, mouse genetics in particular exemplifies the translational aspect of model organism research. **Through research utilizing the mouse as a model for human disease, investigators can *translate* basic biological phenomena into a human health perspective.** For example, mouse models have added to our understanding of human obesity, cancer, cardiovascular disease, diabetes, Parkinson's and Alzheimer's, to name just a few. The value of the mouse as a model organism is derived from the fact that the mouse has similar developmental, physiological, biochemical, and behavioral patterns to humans. It is worth noting that the similarities between human and mouse are supported at the genotypic level - 99% of mouse genes have homologs in humans. Because of the suite of available molecular tools, specifically the long history of making and studying mouse mutants, along with the genomic and phenotypic similarities with humans, advances in mouse genetics continue to be a driving force in a broad range of biomedical research activities.

For more on the scientific utility of mouse knockouts, see the Knockout Mouse Fact Sheet: http://www.genome.gov/12514551

What are the advantages of making the KOMP resource?

A significant number of the 25,000 mouse genes (about 3200) have been knocked out and published. However, many published mice are not readily available to the scientific community (e.g., only 740 unique genes are represented as targeted mutations in the International Mouse Strain Resource). The reason for the restricted availability of these mice is that they have been generated either in individual laboratories or as commercial efforts, and not as a public resource. The limited availability of the mice force a redundancy in production – a single mouse gene is knocked out on average 2.5 times – which presents a large financial burden for the entire biomedical research community. Collaborating with existing efforts, nationally and internationally,

as well as centralizing the process of making new mutants will capitalize on efficiencies of scale. **This will save time and dollars down the road; insure that mice are made available for researchers at relatively low costs and in a timely fashion; completely mutagenize the whole genome more quickly than in the current one-off fashion; and possibly create a platform for normalizing down stream phenotypic analyses.** No longer would a researcher need to invest large sums of grant dollars into generating these reagents, nor run the risk of losing one to two years of research effort if the attempt fails, but could invest the savings in detailed characterization of the mutant mouse and other data generating experiments.

How will KOMP affect peoples' health?

As mentioned above, mouse mutants have served as important models for understanding human disease and developing therapies to treat those conditions. Knockout mutants represent one of the most powerful tools in this endeavor. Because KOMP proposes a comprehensive mutagenesis strategy covering the entire genome, all areas of biomedical research will benefit. This resource will be available sooner than if undertaken by individual laboratories which have not traditionally released mutants until after publication. In the long term, KOMP will lay the ground work for large scale comparative analyses by collecting phenotypic datasets for each mutant. This resource will support rapid identification of genes implicated in different disease models thereby suggesting targets for drug therapies. **The net impact of KOMP will enhance the rapidity and efficiency with which researchers will be able to translate the underlying genetic causes of disease to human health.** Public health will be greatly benefited through the facilitation of biomedical research by making a valuable and important research tool quickly and widely available.

Who are the members of the KOMP Working Group?

NHGRI	http://www.genome.gov/
NCI	http://www.cancer.gov/
NCRR	http://www.ncrr.nih.gov/
NEI	http://www.nei.nih.gov/
NHLBI	http://www.nhlbi.nih.gov/
NIA	http://www.nia.nih.gov/
NIAAA	http://www.niaaa.nih.gov/
NIAID	http://www.niaid.nih.gov/
NIAMS	http://www.niams.nih.gov
NICHD	http://www.nichd.nih.gov/
NIDA	http://www.nida.nih.gov/
NIDCD	http://www.nidcd.nih.gov/
NIDCR	http://www.nidcr.nih.gov/
NIDDK	http://www.niddk.nih.gov/
NIEHS	http://www.niehs.nih.gov/
NIMH	http://www.nimh.nih.gov/
NINDS	http://ninds.nih.gov/

Funding Opportunities:

1. HG-05-007: The Completion of a Comprehensive Mouse Knockout Resource *(Application Receipt Dates: November 22, 2005)*

- ***Important!***
  Amendment 1*: NOT-HG-06-001 (October 6, 2005)*
  Amendment 2*: NOT-HG-06-002 (October 25, 2005)*

- ***FAQs*** *can be found here (November 7, 2005)*

2. DA-06-009: Development and Improvement of Inbred ES Cell Lines for Use in Generation of Mouse Mutants *(Application Receipt Dates: November 22, 2005)*

- ***Important!***
  Amendment 1*: NOT-DA-06-001 (October 14, 2005)*

- ***FAQs*** *can be found here (November 7, 2005)*

3. HG-05-008: A Data Coordination Center for the Knockout Mouse Project (KOMP) *(Application Receipt Dates: November 22, 2005)*

4. Repository and Repatriation RFA coming soon

Future Activities:

As stated in the Banbury report, a comprehensive catalog of ES cells with a null mutation for every gene in the mouse genome would provide the floor upon which additional analyses and experimentation could be done. One of the advantages of KOMP is that the remaining genes would be knocked out in a relatively uniform way, thus facilitating downstream phenotyping in a universal fashion. The uniform molecular biology that would underlie the KOMP mutagenesis strategy would support comparative phenotyping studies, which are at present difficult to perform because each mutant has it's own set of unique molecular variables. The downstream phenotyping events would be comprised of separate tiers:

Tier 1: After generating the ES cells or embryos, mice would be made and run through a broad spectrum of phenotype analyses, such as tissue expression profiling for the mutated gene.

Tier 2: A subset of these animals would then be chosen for further in-depth studies which would include transcriptome analysis and system-specific phenotyping. This would be funded by individual NIH Institutes and Centers according to their own interests and scientific priorities.

Tier 3: Specialized phenotpying would be done in a smaller number of lines which have previously displayed particularly interesting phenotypes. This would also be funded by individual NIH institutes in accordance with their own scientific priorities.

Other related projects:

The Mouse Transcriptome Project:

The Mouse Transcriptome Project is an NIH initiative that is generating a free, public database of gene transcripts for many mouse tissues. Currently, transcriptome data are available on more than 90 tissue samples. These tissue-specific expression data, which are mapped to the mouse genome, are available in a searchable format in the Mouse Reference Transcriptome Database and at the Mouse Reference Transcriptome.

The mouse was chosen for this effort because its genome has been sequenced, because its tissues can be obtained under rigorous quality control conditions, and because of its importance as a model for the study of human biology and disease. For more information and a description of transcriptomes, see http://www.genome.gov/13014330#6.

The Mammalian Gene Collection

The Mammalian Gene Collection is a National Institutes of Health (NIH) initiative that is building a collection of copies of human, mouse and rat mRNA sequences in a form called complementary DNA (cDNA) clones. The project, which is co-led by NHGRI and the National Cancer Institute, is well over half of the way to its goal of providing at least one cDNA clone for every known human and mouse gene.

Researchers can view the cDNA sequence data in a free, public database located at the Mammalian Gene Collection. They can also order copies of these cDNA clones and then insert them into bacterial or mammalian cells, causing the cells to synthesize the proteins encoded by that particular gene transcript. This enables researchers to study the protein's properties in greater detail, as well as to examine the effects that the protein and mutant versions of the protein may have on various cell types.

List of related links and resources:

Domestic

NCBI Mouse Genome Resource Page
http://www.ncbi.nlm.nih.gov/genome/guide/mouse/index.html

Ensemble Mouse Genome Server
http://www.ensembl.org/Mus_musculus/

MGI (Mouse Genome Informatics) http://www.informatics.jax.org/

MMRRC (Mutant Mouse Regional Resource Centers)
http://www.mmrrc.org/

Mouse Genome Browser Gateway (UCSC)
http://genome.ucsc.edu/goldenPath/customTracks/custTracks.html

Bay Genomics http://baygenomics.ucsf.edu/

Neuromouse http://neurosciencesblueprint.nih.gov/

NIDA Mouse Resources
http://www.drugabuse.gov/about/organization/Genetics/mouse/index.html

Mouse Models for Human Cancer Consortium http://emice.nci.nih.gov/

Foreign and International

IGTC (International Gene Trap Consortium) http://www.igtc.org.uk/

IMSR (International Mouse Strain Repository) http://www.informatics.jax.org/imsr/index.jsp

The Wellcome Trust Sanger Institute http://www.sanger.ac.uk

- Sanger (Gene Trap Resource) http://www.sanger.ac.uk/PostGenomics/genetrap/
- Sanger (MICER) http://www.sanger.ac.uk/PostGenomics/mousegenomics/

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